



---

Joanisse, Sophie ORCID logoORCID: <https://orcid.org/0000-0001-9983-9401>, Snijders, Tim, Nederveen, Joshua P and Parise, Gianni (2018) The Impact of Aerobic Exercise on the Muscle Stem Cell Response. Exercise and Sport Sciences Reviews, 46 (3). pp. 180-187. ISSN 0091-6331

---

**Downloaded from:** <https://e-space.mmu.ac.uk/626484/>

**Version:** Accepted Version

**Publisher:** Ovid Technologies (Wolters Kluwer Health)

**DOI:** <https://doi.org/10.1249/jes.0000000000000153>

Please cite the published version

<https://e-space.mmu.ac.uk>

**Heading: Article**

**Accepted: 04/02/2018**

**Editor: Marni D. Boppart, Sc.D., FACSM**

## **The Impact of Aerobic Exercise on the Muscle Stem Cell Response**

Sophie Joannis<sup>1</sup>, Tim Snijders<sup>2</sup>, Joshua P. Nederveen<sup>3</sup>, Gianni Parise<sup>3,4</sup>

<sup>1</sup>School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham

<sup>2</sup>NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University

<sup>3</sup>Department of Kinesiology, McMaster University

<sup>4</sup>Medical Physics and Applied Radiation Sciences, McMaster University

# **The Impact of Aerobic Exercise on the Muscle Stem Cell Response**

Sophie Joannis<sup>1</sup>, Tim Snijders<sup>2</sup>, Joshua P. Nederveen<sup>3</sup>, Gianni Parise<sup>3,4</sup>

<sup>1</sup>School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham

<sup>2</sup>NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University

<sup>3</sup>Department of Kinesiology, McMaster University

<sup>4</sup>Medical Physics and Applied Radiation Sciences, McMaster University

## **Corresponding author**

Dr. Gianni Parise

Departments of Kinesiology and Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, Ontario, Canada L8S 4L8.

E-mail: [pariseg@mcmaster.ca](mailto:pariseg@mcmaster.ca); Telephone: 905 525 9140 ext. 27353

**Conflict of interest:** The authors declare no conflict of interest

## **Abstract**

Satellite cells are indispensable for skeletal muscle repair and regeneration and are associated with muscle growth in humans. Aerobic exercise training results in improved skeletal muscle health also translating to an increase in satellite cell pool activation. We postulate that aerobic exercise improves satellite cell function in skeletal muscle.

**Summary for Table of Contents:** The importance of aerobic exercise training on improved satellite cell function.

## **Key Points**

- Skeletal muscle specific stem cells are termed satellite cells and are indispensable for skeletal muscle repair and regeneration.
- In addition to the more traditional studies investigating the impact of resistance exercise on satellite cells, recent studies suggest that satellite cells may also respond to endurance exercise.
- As satellite cells are imperative to skeletal muscle regeneration, heightened activation of the satellite cell pool following aerobic exercise training may render skeletal muscle repair more efficient following injury.
- We aim to discuss the potential of aerobic exercise to improve the capacity of skeletal muscle to repair and remodel via improved satellite cell function.

**Key Words:** aerobic exercise; skeletal muscle; satellite cells; regeneration; repair

## INTRODUCTION

Skeletal muscle is one of the largest organs of the human body and plays an essential role in whole body locomotion. It also acts as an important nutrient store and serves as a source of glucose disposal, maintaining whole body homeostasis. Skeletal muscle possesses a remarkable plasticity and can respond to a wide range of stimuli such as injury, damage and exercise. Regular exercise results in improvements in various metabolic and structural aspects of skeletal muscle health. Resistance exercise training has long been associated with increases in skeletal muscle mass characterized by increases in muscle fibre cross sectional area (CSA) (1, 2). Alternatively, aerobic exercise training, including moderate intensity continuous training (MICT), high intensity interval training (HIT) and sprint interval training (SIT) (3), is associated not only with structural remodelling of muscle fibres towards a more oxidative phenotype but also with increases in mitochondrial protein content and function, and increased capillary density (4, 5). Over the years extensive research has focused on understanding the molecular basis for structural and functional adaptations that occur in skeletal muscle following exercise training.

Satellite cells (SC) are muscle specific stem cells that are essential in skeletal muscle repair and regeneration (6, 7). Specifically, SC reside between the sarcolemma and the basal lamina, an area referred to as the SC niche (8). The muscle fibre to which the SC is associated also composes part of the niche and thus SC respond to various signals originating from the muscle fibre (8). When SC become activated, they proliferate and differentiate, eventually fusing to existing muscle fibres and donating their nuclei and thereby supporting skeletal muscle fibre repair (7) and growth (9-12). It is important to note, however, that upon activation a subset of SC will revert to quiescence thereby maintaining the SC pool (13). The extent to which SC facilitate

exercise-induced adaptations is not clear, but further studies are warranted and of keen interest to investigators in the field of exercise science.

SC have the ability to fuse to muscle fibres, and due to this reason it has long been believed that SC may play a role in mediating increases in muscle fibre size such as those observed following resistance exercise training (2, 9-12). This notion is supported by the myonuclear domain theory, which suggests that each myonucleus governs a particular volume of cytoplasm. Once the volume of a cell exceeds the capacity of an individual nucleus (i.e. an increase in muscle fibre size) the addition of new nuclei is necessary to support a larger cell volume (14). As skeletal muscle fibres are post-mitotic in nature, the addition of new nuclei requires fusion of SC to existing muscle fibres. This theory was originally supported by work in rodent models in which SC were ablated by gamma irradiation. Skeletal muscle that was void of SC did not respond to overload-induced hypertrophy whereas control, non-irradiated, rodents experienced significant hypertrophy (15, 16). However, recent work has challenged common dogma that SC are necessary for inducing muscle fibre hypertrophy. A novel mouse model was developed that achieved near complete ablation of SC in mature skeletal muscle. In this model, SC ablated animals maintained the ability to respond to various hypertrophic stimuli such as 2 and 6 weeks of overload via synergist ablation (6) and 14 days of reloading preceded by 14 days of atrophy induced via hindlimb suspension (17). This suggests that, at least in rodents, SC are not necessary for inducing skeletal muscle fibre hypertrophy. However, SC seem to be required to maintain muscle growth as muscle hypertrophy is attenuated in SC depleted rodents following 8 weeks of overload (18). To further the debate on whether SC are necessary to mediate this process a more recent study using the same mouse model as described above, albeit in younger mice, reported impaired skeletal muscle hypertrophy following 2 weeks of overload

induced hypertrophy (19). Although a highly debated topic when examining data from rodent models, an increase in muscle fibre size has been associated with an expansion of the SC pool in humans (20). This evidence would support the notion that, in humans, nuclear addition is an important part of muscle hypertrophy, consistent with theory that SC contribute to muscle growth. It is, however, important to note that recent work in humans has described an increase in muscle fibre CSA without an apparent concomitant increase in the SC pool (18).

Less explored is the impact of aerobic exercise training on the SC pool and the subsequent impact of this event on muscle adaptation in humans. We hypothesize that aerobic exercise training may improve SC function, directly impacting the ability of skeletal muscle to respond to stimuli such as injury and immobilization. The impact of resistance exercise and aerobic exercise training on the SC pool in human skeletal muscle is described in Figure 1. The following review will discuss advances regarding the effect of aerobic exercise training on SC function.

## **AEROBIC EXERCISE TRAINING AND ITS EFFECT ON SATELLITE CELL-MEDIATED MUSCLE GROWTH AND REMODELLING**

Aerobic exercise training in rodents consistently results in an increase in SC content (21-25). In addition, work in rodents suggests that exercise intensity may be important in expanding the SC pool (22). The fact that SC expansion can occur in the absence of increased myofiber CSA and muscle mass in some instances (21-23, 25) suggests an important role for SC in muscle plasticity and adaptation outside the traditional role of promoting muscle growth. The results of studies discussed are summarized in Table 1.

The SC response to aerobic exercise in humans has not been as extensively studied and the results are much less consistent than that observed in rodent models. SC content in skeletal muscle has been observed to be positively correlated with  $\text{VO}_{2\text{max}}$ , suggesting that SC may play a role in maintaining muscle fibre health/function in individuals with a high aerobic capacity (26). However, this study did not take into account fibre CSA and it may be possible that subjects with a greater  $\text{VO}_{2\text{max}}$  also had greater fibre CSA and this could account for the association between  $\text{VO}_{2\text{max}}$  and SC content. Some studies report an increase in SC content in older adults following 14 weeks of interval training, although an increase in type IIa fibre CSA was also observed (27, 28). Therefore, the increase in SC content may have occurred in order to mediate fibre hypertrophy.

More recent work has described an increase in SC associated with type I muscle fibres in middle aged adults following 12 weeks of MICT (18, 29). Interestingly, both studies report an increase in CSA of all fibre types whereas an expansion of the SC pool was only observed in type I fibres (18, 29). In addition, an endurance training program that did not induce an increase in muscle fibre size also did not result in an increase in SC content in older participants with type 2 diabetes (30). We have recently demonstrated that there is no apparent expansion in the basal SC pool following 6 weeks of various forms of endurance exercise, concomitant with no observed increase in muscle fibre CSA (31, 32). Although we did not observe an increase in overall SC content we demonstrated that following 6 weeks of aerobic interval training, there was an increase in SC associated with hybrid muscle fibres, muscle fibres expressing both myosin heavy chain type I and II, only (31). It is, however, important to note the proportion of hybrid fibres at baseline was very low. Following aerobic interval training there was a trend for an increase in hybrid fibres and, a greater proportion of these fibres had centrally located nuclei,



a hallmark of repairing/remodelling fibres. We also observed a high number of SC associated with fibres expressing neonatal MHC (31). To further evaluate the response of SC to aerobic exercise we determined the effect of either 6 weeks of MICT or 2 different SIT protocols, varying in interval duration. We demonstrated that there was an increase in SC activity (increase in MyoD expression as evidence of activation) without an apparent expansion of the Pax7<sup>+</sup> pool in the absence of hypertrophy following all three aerobic exercise training programs (32).

Together these results highlight the capacity for SC to respond to aerobic exercise and the potential for SC to engage in a training response appropriate for this type of stimulus. Results from human studies are much more variable than what is observed when rodent models are employed as is highlighted in Table 1. Any discrepancies observed are likely due to the variable ages of the populations employed in addition to a variety of aerobic training programmes.

## **THE IMPACT OF AEROBIC EXERCISE ON SC FUNCTION**

SC are indispensable for skeletal muscle regeneration. Several rodent models have demonstrated severe impairment in muscle regeneration when SC are abolished from skeletal muscle (6, 7) Aerobic exercise results in increased mitochondrial biogenesis and capillary density. The following sections will discuss the potential mechanisms by which aerobic exercise can modulate SC function.

### **The importance of mitochondrial biogenesis in the regulation of SC function**

*In vitro* work has demonstrated an impairment in myotube formation when mitochondrial synthesis is inhibited, although gene expression of both MyoD and myogenin, genes related to myogenesis remained unaffected (33). These early findings suggest that mitochondrial content is

important for myoblast differentiation. Mitochondrial biogenesis is increased during skeletal muscle regeneration (34), thus implicating mitochondria as a contributing factor in regeneration. Work in a rat model demonstrated that following gastrocnemius muscle injury, a marked reduction in mitochondrial functionality was observed. However, by restoring mitochondrial function via administration of polycistronic RNAs, which encoded the heavy strand of the rat mitochondrial genome into the injured muscle, SC proliferation was increased, accompanied by improved muscle regeneration (34), suggesting that mitochondrial function may have a considerable role in myogenesis. To further support the importance of mitochondrial biogenesis in SC function, isolated SC demonstrating enhanced activation, defined by cells that entered the cell cycle more quickly following isolation, have higher levels of mitochondrial activity and ATP concentration compared to those with lower activation (35). In addition, SC from mice that underwent a short-term calorie restricted diet had an increased oxygen consumption rate, mitochondrial content and mitochondrial protein content (36). SC also experienced improved myogenic function and together this translated to improved muscle repair (36).

The ablation of SIRT1, a modulator of mitochondrial homeostasis, in skeletal muscle of rodents resulted in impaired skeletal muscle regeneration further supporting the role of mitochondria in regeneration (37). Supplementation with nicotinamide riboside (NR), an NAD(+) precursor, increased SC content in both young and old rodents and accelerated muscle regeneration following injury, however this improvement was not observed in rodents in which SIRT1 was not expressed in skeletal muscle indicating that NR supplementation improved SC function in a SIRT1 dependent manner (37). Although not directly employing exercise as an intervention this data further supports the role of mitochondria in mediating SC function. These results suggest that aerobic exercise, via increased mitochondrial content and function, may

potentially improve SC function. Improved SC function may re-establish muscle fibre structure and function in a more efficient manner.

### **The importance of the vasculature in the regulation of SC function**

Skeletal muscle perfusion is critical for the maintenance of skeletal muscle health. Adequate fibre perfusion is necessary to provide skeletal muscle with oxygen, nutrients and various growth factors, while carrying away carbon dioxide and metabolic by-products (38). A hallmark adaptation associated with aerobic exercise training is an increase in skeletal muscle capillarization (5). In addition to maintenance of muscle health, revascularization is an important part of the regenerative/repair process following injury to skeletal muscle (39). It is well established that there is a spatial relationship between SC and capillaries in humans. Active SC are located at a closer proximity to capillaries compared to quiescent SC (40). In addition, it is known that there is 'cross-talk' between SC and endothelial cells (41, 42). Therefore, the microvasculature of the skeletal muscle can impact SC function. Not only does structure of the microvasculature in skeletal muscle affect SC function but key signalling molecules such as myostatin, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and insulin-like growth factor 1 (IGF-1) amongst others, present in general circulation may interact with the SC niche and impact SC function (43). Exercise has been shown to result in increased circulating levels of various cytokines such as a number of interleukins (IL-1, IL-6, IL-8, IL-10) and tumor necrosis factor  $\alpha$  (44). The term 'myokine' has recently been coined and describes a cytokine released by skeletal muscle. Myokines are produced following exercise and can act in both a paracrine or endocrine manner altering the SC microenvironment (45). IL-6 is the most widely studied myokine and its expression is drastically increased following exercise (46).

Interestingly, IL-6 can be classified as both a pro- and anti-inflammatory cytokine (47) and has been associated with SC proliferation in humans following eccentric muscle contractions (48). Recent work has demonstrated that basal skeletal muscle capillarization in older adults may be important in promoting skeletal muscle hypertrophy following a resistance exercise training programme (49). Older adults were compared based on their extent of type II fibre capillary to fibre perimeter exchange index (CFPE) and only those considered to have a 'high' CFPE had an increase in fibre size and SC content following 24 weeks of resistance training. Although the results of this study are not directly linked to aerobic exercise; aerobic exercise does result in increased capillary density thereby potentially reducing the distance between capillaries and SC and maximizing the outcomes of a resistance exercise training programme.

Administration of VEGF, a primary driver of angiogenesis, following injury induced via ischemia results in improved skeletal muscle regeneration in addition to improving angiogenic and myogenic properties of the muscle (50). *In vitro* results have demonstrated that VEGF treatment promotes myotube hypertrophy and facilitates differentiation (51). Aerobic exercise training results in increased VEGF mRNA expression in skeletal muscle (52), therefore another potential mechanism by which aerobic exercise improves SC function may be by increasing muscle capillarization and VEGF mRNA expression.

Endurance exercise training therefore has the ability to improve SC function in various ways. These proposed mechanisms are summarized in Figure 2. For example, endurance exercise may increase mitochondrial protein content and function within SC, increase capillarization of skeletal muscle thereby reducing the distance between SC and capillaries maximizing the ability of SC to respond to stimuli and also by inducing changes in the systemic environment ultimately altering the SC microenvironment (53, 54).

## **FUNCTIONAL IMPLICATIONS OF SATELLITE CELL ADAPTATION TO AEROBIC EXERCISE**

Considering the evidence presented above we hypothesize that aerobic exercise improves SC function. The overall health benefits of endurance exercise training are numerous as are the adaptations in skeletal muscle. Although these adaptations are not limited to the SC and its niche, improved SC function can also improve skeletal muscle health and function. Some groups have reported impaired regeneration in old rodents (55-57) while others report normal regeneration (58-60). Although age-associated changes in SC content have been observed, skeletal muscle from old animals retains the ability to positively respond to aerobic exercise (23-25). We have recently demonstrated that old mice that have exercise trained prior to inducing skeletal muscle injury have an improved ability to regenerate skeletal muscle compared to sedentary age-matched animals. The improvement in skeletal muscle regeneration may be due to an increase in the basal SC pool, as SC are indispensable for muscle regeneration (23). Specifically, greater SC content in old exercised compared to sedentary animals may have, in part, been due to an increase in mitochondrial content and function observed in these animals ultimately improving the muscle's ability to regenerate. Accelerated muscle regeneration in these animals points to not only an increase in SC content and potentially function, but also to an improvement in functional outcome as evidenced by a complete re-establishment of muscle fibre size. Although, translating findings from rodent studies to humans must be done with caution these results support the notion that aerobic exercise improves SC function.

Disuse models in humans have convincingly demonstrated an inability to re-establish muscle fibre CSA following remobilization and that SC content is reduced following periods of disuse in old adults (61). A reduction in CSA has been reported as early as 7 days following

immobilization (62). These results are similarly reflected in rodent models, which demonstrated impaired early muscle regeneration (56, 57). Impaired early regeneration may preclude the muscle from ever fully regenerating. Although, the process of re-establishing muscle fibre size following a period of immobilization is different than re-establishing muscle fibre size following injury, the work completed in rodents suggests that older adults that exercise may be able to better recover from periods of immobilization. The ability for an older adult to re-establish muscle fibre size following a period of immobilization is essential in delaying the gradual onset of age-associated muscle loss.

The concept of ‘muscle memory’ has garnered much attention in recent years. Previous work in rodent models has demonstrated that skeletal muscle retains myonuclei acquired during a period of overload induced hypertrophy when faced with a subsequent period of muscle loss due to denervation. In addition, animals that had previously undergone overload induced hypertrophy were, to an extent, protected from the denervation-induced muscle loss (63). In line with these findings, rodents that had previously been administered testosterone responded more robustly to a period of overload-induced hypertrophy compared to animals who had not been exposed to testosterone (64). Recent work has explored whether human skeletal muscle possess an enhanced ability to respond to hypertrophic stimuli if it has been exposed to an earlier period of hypertrophy. Here, the authors demonstrate that resistance training results in an increase in lean mass which is reduced to similar levels to baseline following un-loading (65). Interestingly, lean mass is further increased following a subsequent period of resistance training. DNA methylation was assessed following the initial period of resistance training, following the unloading period and again following the subsequent resistance training period. A widespread hypomethylation was observed suggesting that skeletal muscle seems to possess a ‘memory’ of

earlier periods of hypertrophy (65). Taken together these results highlight that a type of ‘muscle’ or ‘myonuclear-memory’ may exist and that prior resistance exercise may better enable the muscle to respond to various anabolic stimuli such as reloading following a period of inactivity. To our knowledge this is the first study to investigate ‘muscle-memory’ following an anabolic stimulus such as resistance training in humans. How this may affect the ability of humans who have had previous exercise training to better respond to periods of muscle loss such as severe step reduction or immobilization and whether this ‘memory’ is maintained with age and to what extent remains to be determined but is an interesting avenue for future research.

We have previously demonstrated that the extent of muscle fibre capillarization may be an important factor in mediating the extent of hypertrophy in older adults (49). No observable increase in muscle fibre size or SC content was observed in older adults with a relatively low capillarization of type II muscle fibres prior to the onset of a resistance training programme (49). The results of this study suggest that skeletal muscle perfusion must be adequate to support an increase in muscle fibre size and this may be due to an expansion of the SC pool. Therefore, maximizing skeletal muscle capillarization may better support the ability of skeletal muscle to respond to hypertrophic stimuli such as resistance training. Aerobic exercise training results in an increased capillary density in skeletal muscle, which may improve SC function ultimately maximizing increases in muscle fibre size following resistance exercise. Although resistance exercise is the gold standard for increasing muscle mass, aerobic exercise in older individuals may not only improve cardio metabolic health but may also improve skeletal muscle health and its ability to repair/regenerate following periods of disuse – potentially through improved SC function. Recent work has demonstrated that endurance exercise training is able to alter the acute SC response to resistance exercise (29). Following a bout of acute resistance exercise an increase

in SC associated with type I muscle fibres was observed. However, this acute increase after a bout of resistance exercise was no longer observed following 12 weeks of endurance training (29). Although this study does not directly address how endurance exercise affects SC biology it further supports the notion that endurance exercise can directly impact SC function.

## **CONCLUSION**

The vast benefits of exercise and its ability to improve health in a wide range of populations are widely accepted. In human work, resistance exercise training has long been associated with an increase in SC content. More recently, a focus has been placed on understanding the effects of aerobic exercise on SC function in skeletal muscle. We postulate that endurance exercise is able to improve SC function via mechanisms described above and are outlined in Figure 2. In addition to the canonical role for SC in mediating muscle growth, we hypothesize that endurance exercise is able to improve muscle regeneration in skeletal muscle of rodents likely due to various factors, one of which may be a direct improvement in SC function. The ability of aerobic exercise to modulate SC function is an important finding and may be beneficial in improving skeletal muscle health in various muscle wasting states such as aging. Future work should be aimed at further understanding the ability of aerobic exercise to improve SC health in skeletal muscle.



## **Acknowledgments**

Dr. Gianni Parise was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Grant (1455843), JP Nederveen by a NSERC Canadian Graduate Scholarship (CGS-D). We would like to thank Jessica Blackwood for her assistance in the preparation of the figures.

## References

1. Kosek DJ, Kim JS, Petrella JK, Cross JM, Bamman MM. Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. *Journal of applied physiology*. 2006;101(2):531-44.
2. Petrella JK, Kim JS, Cross JM, Kosek DJ, Bamman MM. Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women. *American Journal of Physiology-Endocrinology and Metabolism*. 2006;291(5):E937-E46.
3. MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *The Journal of physiology*. 2016; 595(9):2915-30.
4. Gibala MJ, Little JP, MacDonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology*. 2012;590(5):1077-84.
5. Hoppeler H, Howald H, Conley K et al. Endurance training in humans: aerobic capacity and structure of skeletal muscle. *Journal of Applied Physiology*. 1985;59(2):320-7.
6. McCarthy JJ, Mula J, Miyazaki M et al. Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. *Development*. 2011;138(17):3657-66.
7. Sambasivan R, Yao R, Kissenpfennig A et al. Pax7-expressing satellite cells are indispensable for adult skeletal muscle regeneration. *Development*. 2011;138(17):3647-56.
8. Kuang S, Gillespie MA, Rudnicki MA. Niche regulation of muscle satellite cell self-renewal and differentiation. *Cell stem cell*. 2008;2(1):22-31.
9. Bellamy LM, Joannis S, Grubb A et al. The acute satellite cell response and skeletal muscle hypertrophy following resistance training. *PLoS One*. 2014;9(10):e109739.

10. Kadi F, Thornell L-E. Concomitant increases in myonuclear and satellite cell content in female trapezius muscle following strength training. *Histochemistry and cell biology*. 2000;113(2):99-103.
11. Mackey AL, Andersen LL, Frandsen U, Sjøgaard G. Strength training increases the size of the satellite cell pool in type I and II fibres of chronically painful trapezius muscle in females. *The Journal of physiology*. 2011;589(22):5503-15.
12. Petrella JK, Kim JS, Mayhew DL, Cross JM, Bamman MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. *Journal of applied physiology*. 2008;104(6):1736-42.
13. Rudnicki MA, Le Grand F, McKinnell I, Kuang S. The molecular regulation of muscle stem cell function. *Cold Spring Harb Symp Quant Biol*. 2008;73:323-31.
14. Allen DL, Roy RR, Edgerton VR. Myonuclear domains in muscle adaptation and disease. *Muscle & nerve*. 1999;22(10):1350-60.
15. Adams GR, Caiozzo VJ, Haddad F, Baldwin KM. Cellular and molecular responses to increased skeletal muscle loading after irradiation. *American Journal of Physiology-Cell Physiology*. 2002;283(4):C1182-C95.
16. Rosenblatt JD, Parry DJ. Gamma irradiation prevents compensatory hypertrophy of overloaded mouse extensor digitorum longus muscle. *Journal of Applied Physiology*. 1992;73(6):2538-43.
17. Jackson JR, Mula J, Kirby TJ et al. Satellite cell depletion does not inhibit adult skeletal muscle regrowth following unloading-induced atrophy. *American Journal of Physiology-Cell Physiology*. 2012;303(8):C854-C61.

18. Fry CS, Noehren B, Mula J et al. Fibre type-specific satellite cell response to aerobic training in sedentary adults. *The Journal of physiology*. 2014;592(12):2625-35.
19. Egner IM, Bruusgaard JC, Gundersen K. Satellite cell depletion prevents fiber hypertrophy in skeletal muscle. *Development*. 2016;143(16):2898-906.
20. Snijders T, Nederveen JP, McKay BR et al. Satellite cells in human skeletal muscle plasticity. *Frontiers in physiology*. 2015;6:283.
21. Kurosaka M, Naito H, Ogura Y, Kojima A, Goto K, Katamoto S. Effects of voluntary wheel running on satellite cells in the rat plantaris muscle. *J Sports Sci Med*. 2009;8(1):51-7.
22. Kurosaka M, Naito H, Ogura Y, Machida S, Katamoto S. Satellite cell pool enhancement in rat plantaris muscle by endurance training depends on intensity rather than duration. *Acta Physiologica*. 2012;205(1):159-66.
23. Joannis S, Nederveen JP, Baker JM, Snijders T, Iacono C, Parise G. Exercise conditioning in old mice improves skeletal muscle regeneration. *The FASEB Journal*. 2016;30(9):3256-68.
24. Shefer G, Rauner G, Stuelsatz P, Benayahu D, Yablonka-Reuveni Z. Moderate-intensity treadmill running promotes expansion of the satellite cell pool in young and old mice. *FEBS Journal*. 2013;280(17):4063-73.
25. Shefer G, Rauner G, Yablonka-Reuveni Z, Benayahu D. Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise. *PloS one*. 2010;5(10):e13307.
26. Macaluso F, Myburgh K. Current evidence that exercise can increase the number of adult stem cells. *Journal of muscle research and cell motility*. 2012;33(3-4):187-98.

27. Verney J, Kadi F, Charifi N et al. Effects of combined lower body endurance and upper body resistance training on the satellite cell pool in elderly subjects. *Muscle & nerve*. 2008;38(3):1147-54.
28. Charifi N, Kadi F, Féasson L, Denis C. Effects of endurance training on satellite cell frequency in skeletal muscle of old men. *Muscle & nerve*. 2003;28(1):87-92.
29. Murach KA, Walton RG, Fry CS et al. Cycle training modulates satellite cell and transcriptional responses to a bout of resistance exercise. *Physiological Reports*. 2016;4(18):e12973.
30. Snijders T, Verdijk LB, Hansen D, Dendale P, van Loon LJ. Continuous endurance-type exercise training does not modulate satellite cell content in obese type 2 diabetes patients. *Muscle & nerve*. 2011;43(3):393-401.
31. Joannis S, Gillen JB, Bellamy LM et al. Evidence for the contribution of muscle stem cells to nonhypertrophic skeletal muscle remodeling in humans. *The FASEB Journal*. 2013;27(11):4596-605.
32. Joannis S, McKay BR, Nederveen JP et al. Satellite cell activity, without expansion, after nonhypertrophic stimuli. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2015;309(9):R1101-R11.
33. Hamai N, Nakamura M, Asano A. Inhibition of Mitochondria! Protein Synthesis Impaired C2C12 Myoblast Differentiation. *Cell structure and function*. 1997;22(4):421-31.
34. Jash S, Adhya S. Induction of muscle regeneration by RNA-mediated mitochondrial restoration. *The FASEB Journal*. 2012;26(10):4187-97.

35. Rocheteau P, Gayraud-Morel B, Siegl-Cachedenier I, Blasco MA, Tajbakhsh S. A subpopulation of adult skeletal muscle stem cells retains all template DNA strands after cell division. *Cell*. 2012;148(1):112-25
36. Cerletti M, Jang YC, Finley LW, Haigis MC, Wagers AJ. Short-term calorie restriction enhances skeletal muscle stem cell function. *Cell stem cell*. 2012;10(5):515-9.
37. Zhang H, Ryu D, Wu Y, Gariani K, Wang X, Luan P, et al. NAD(+) repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science*. 2016;352(6292):1436-43.
38. Timmerman KL, Lee JL, Dreyer HC et al. Insulin stimulates human skeletal muscle protein synthesis via an indirect mechanism involving endothelial-dependent vasodilation and mammalian target of rapamycin complex 1 signaling. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(8):3848-57.
39. Bodine-Fowler S. Skeletal muscle regeneration after injury: an overview. *Journal of voice*. 1994;8(1):53-62.
40. Nederveen JP, Joannis S, Snijders T et al. Skeletal muscle satellite cells are located at a closer proximity to capillaries in healthy young compared with older men. *Journal of cachexia, sarcopenia and muscle*. 2016;7(5):547-54.
41. Bellamy LM, Johnston AP, De Lisio M, Parise G. Skeletal muscle-endothelial cell cross talk through angiotensin II. *American Journal of Physiology-Cell Physiology*. 2010;299(6):C1402-C8.
42. Chazaud B, Sonnet C, Lafuste P et al. Satellite cells attract monocytes and use macrophages as a support to escape apoptosis and enhance muscle growth. *The Journal of cell biology*. 2003;163(5):1133-43.

43. Nederveen JP, Joannis S, Snijders T, Parise G. The Influence and Delivery of Cytokines and their Mediating Effect on Muscle Satellite Cells. *Current Stem Cell Reports*. 2017;3(3):192-201.
44. Pedersen BK. Exercise and cytokines. *Immunology And Cell Biology*. 2000;78:532.
45. Pedersen BK. Exercise-induced myokines and their role in chronic diseases. *Brain, behavior, and immunity*. 2011;25(5):811-6.
46. Pedersen BK. Special feature for the Olympics: effects of exercise on the immune system: exercise and cytokines. *Immunol Cell Biol*. 2000;78(5):532-5.
47. Pedersen BK. Muscles and their myokines. *The Journal of experimental biology*. 2011;214(Pt 2):337-46.
48. Toth KG, McKay BR, De Lisio M, Little JP, Tarnopolsky MA, Parise G. IL-6 induced STAT3 signalling is associated with the proliferation of human muscle satellite cells following acute muscle damage. *PLoS One*. 2011;6(3):e17392.
49. Snijders T, Nederveen JP, Joannis S et al. Muscle fibre capillarization is a critical factor in muscle fibre hypertrophy during resistance exercise training in older men. *Journal of Cachexia, Sarcopenia and Muscle*. 2017; 8(2):267-76.
50. Borselli C, Storrie H, Benesch-Lee F, Shvartsman D, Cezar C, Lichtman JW, et al. Functional muscle regeneration with combined delivery of angiogenesis and myogenesis factors. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(8):3287-92.
51. Bryan BA, Walshe TE, Mitchell DC, Havumaki JS, Saint-Geniez M, Maharaj AS, et al. Coordinated vascular endothelial growth factor expression and signaling during skeletal myogenic differentiation. *Molecular biology of the cell*. 2008;19(3):994-1006.

52. Gavin TP, Ruster RS, Carrithers JA, Zwetsloot KA, Kraus RM, Evans CA, et al. No difference in the skeletal muscle angiogenic response to aerobic exercise training between young and aged men. *J Physiol.* 2007;585(Pt 1):231-9.
53. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *Journal of applied physiology.* 2005;98(4):1154-62.
54. Franceschi C, Capri M, Monti D et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mechanisms of ageing and development.* 2007;128(1):92-105.
55. Sadeh M. Effects of aging on skeletal muscle regeneration. *Journal of the neurological sciences.* 1988;87(1):67-74.
56. Brack AS, Conboy MJ, Roy S et al. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. *Science.* 2007;317(5839):807-10.
57. Conboy IM, Conboy MJ, Smythe GM, Rando TA. Notch-mediated restoration of regenerative potential to aged muscle. *Science.* 2003;302(5650):1575-7.
58. Lee AS, Anderson JE, Joya JE et al. Aged skeletal muscle retains the ability to fully regenerate functional architecture. *Bioarchitecture.* 2013;3(2):25-37.
59. Shavlakadze T, McGeachie J, Grounds MD. Delayed but excellent myogenic stem cell response of regenerating geriatric skeletal muscles in mice. *Biogerontology.* 2010;11(3):363-76.
60. Smythe G, Shavlakadze T, Roberts P, Davies M, McGeachie J, Grounds M. Age influences the early events of skeletal muscle regeneration: studies of whole muscle grafts transplanted between young (8 weeks) and old (13–21 months) mice. *Experimental gerontology.* 2008;43(6):550-62.



61. Suetta C, Frandsen U, Mackey A et al. Ageing is associated with diminished muscle re-growth and myogenic precursor cell expansion early after immobility-induced atrophy in human skeletal muscle. *The Journal of physiology*. 2013;591(15):3789-804.
62. Hvid LG, Suetta C, Nielsen JH et al. Aging impairs the recovery in mechanical muscle function following 4days of disuse. *Experimental gerontology*. 2014;52:1-8.
63. Bruusgaard JC, Johansen IB, Egner IM, Rana ZA, Gundersen K. Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(34):15111-6.
64. Egner IM, Bruusgaard JC, Eftestol E, Gundersen K. A cellular memory mechanism aids overload hypertrophy in muscle long after an episodic exposure to anabolic steroids. *J Physiol*. 2013;591(24):6221-30.
65. Seaborne RA, Strauss J, Cocks M, Shepherd S, O'Brien TD, van Someren KA, et al. Human Skeletal Muscle Possesses an Epigenetic Memory of Hypertrophy. *Scientific reports*. 2018;8(1):1898.

## Figure legend

**Figure 1. The proposed effect of resistance and aerobic exercise training on the satellite cells (SC) pool in humans.** In a homeostatic physiological state (A) each myonucleus governs a set volume of cytoplasm, referred to as the myonuclear domain. Resistance exercise training results in increased muscle fibre cross sectional area (CSA) and SC content (B). To maintain the myonuclear domain it is believed that SC fuse to growing muscle fibres 'donating' their nuclei to support this growth. Aerobic exercise training results in a shift towards a more oxidative phenotype characterized by an increased proportion of type I and hybrid muscle fibres, with no increase in muscle fibre CSA (C). An increase in SC content is not observed with aerobic exercise training. However, an increase in the number of active SC and a greater number of SC associated with hybrid compared to type I and II muscle fibres is observed following aerobic exercise training (C).

**Figure 2. Hypothetical model for the role of aerobic exercise to improve satellite cell (SC) function.** We have demonstrated an increase in SC activation following aerobic exercise training (A). Blue cells represent myonuclei whereas green cells represent fused SC or newly incorporated nuclei. Aerobic exercise also results in increased skeletal muscle capillarization (B) and mitochondrial biogenesis (C). Active SC reside in closer proximity to capillaries in comparison to quiescent SC (B). Aerobic exercise has the ability to modulate the circulating systemic environment impacting the SC microenvironment; increased capillarization may increase the exposure of SC to key signalling molecules found in circulation, depicted as the dotted line surrounding capillaries (B). We propose that aerobic exercise improves SC function via increased skeletal muscle vascularisation and mitochondrial biogenesis. Increased SC activation due to aerobic exercise training may improve the ability of muscle to repair itself following injury (D).

Figure 1

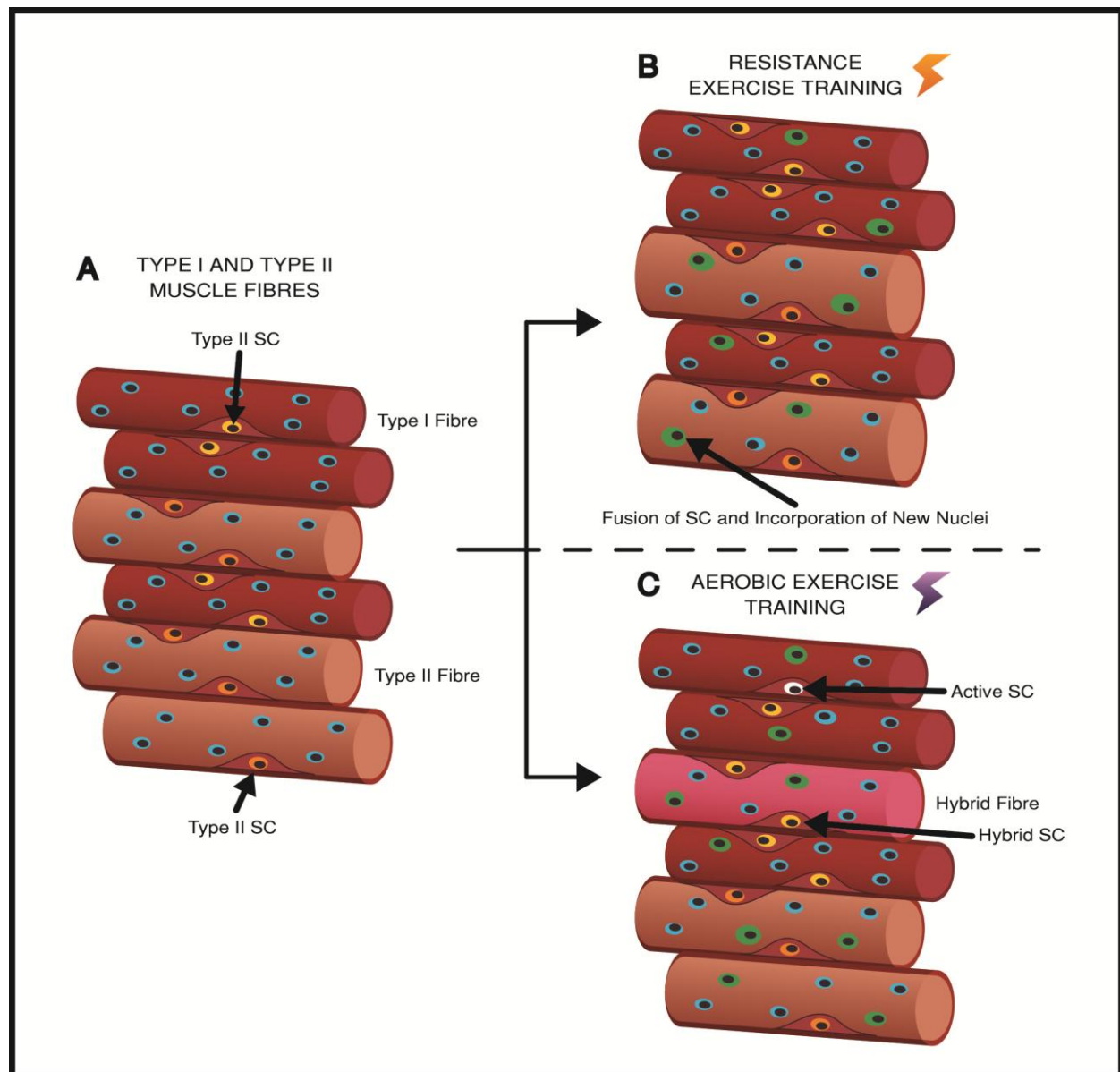


Figure 2

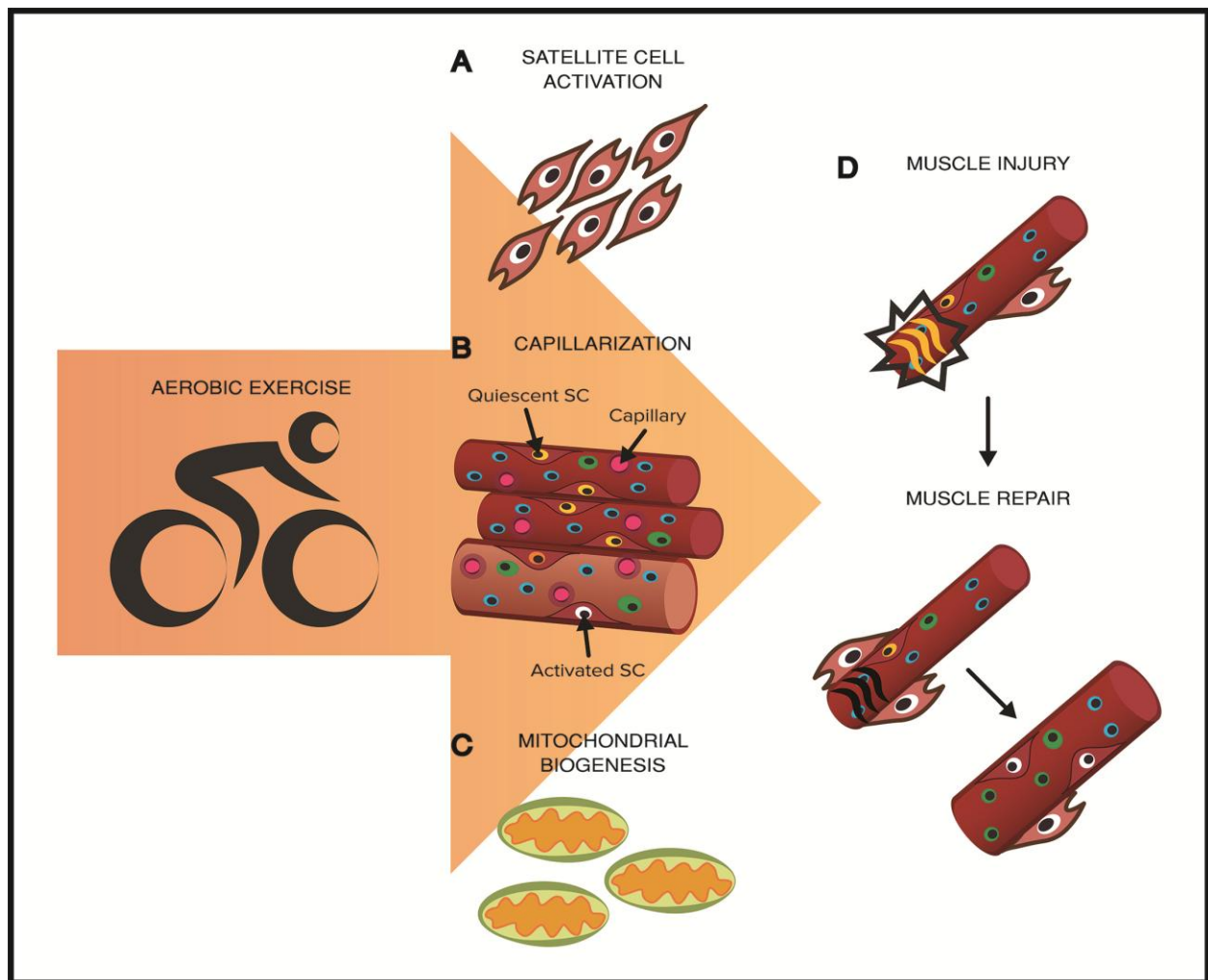


Table. Summary of studies in human and rodents describing the satellite cell (SC) response to aerobic exercise training

Species	Age	Exercise Type	SC response	Reference
Human, male (n=10)	73±4 yr	Concurrent training, 14 wk, 3 d/wk  END training on cycle ergometer: three bouts of 12 min consisting of two sequences of 4 min @ 75%-85% HR <sub>max</sub> followed by 1 min interval @ 80%-95% HR <sub>max</sub> followed by active recovery	++ SC/Type II fiber  ++SC/total fiber	28
Human, male (n=11)	73±3 yr	Interval training, 14 wk, 4 d/wk, on cycle ergometer: seven bouts of 4 min @ 65%-75% $\dot{V}O_{2peak}$ followed by 1 min @ 85%-95% $\dot{V}O_{2peak}$	++ SC/total fiber	29
Human, obese type 2 diabetic males (n=15)	61±6 yr	Endurance exercise, 6 months, 3 d/wk, walking, cycling and cross-country skiing	No change in SC/Type I fiber  No change in SC/Type II fiber	31

		type exercise: total time of 40 min @ 75%  2peak		
Human, overweight females (n=15)	27±8 yr	HIT, 6 wk, 3 d/wk, on cycle ergometer: 10 x 60s bouts of cycling @ 90% HR <sub>max</sub> interspersed with 60s of recovery	No change in SC/Type I fiber  No change SC/Type II fiber  ++SC/Hybrid fiber	32
Human, overweight males (n=6) and females (n=17)	47.6 ± 8 yr	END, 12 wk, 3 d/wk on cycle ergometer: 45 min @ 70% HR reserve	No change in SC/Type II fiber  ++SC/Type I fiber  ++SC/Total fiber	19
Human, overweight/obese men (n=7) and women (n=7)	Men: 29±9 yr  Women: 29±2 yr	SIT, 6 wk, 3 d/wk on cycle ergometer: 3 x 20s sprint against 0.05 kg/kg body mass  interspersed by 2 min  low intensity cycling	No change in SC/Type I fiber  No change in SC/Type II fiber  ++ Pax7+ /MyoD+ cells/Fiber (active SC)  ++ Pax7- /MyoD+ cells/Fiber (differentiating SC)	33
Human, males and females (n=10)	21±2 yr	SIT, 6 wk, 4 d/wk on cycle ergometer: 8 x 20s intervals at 170% at  O <sub>2peak</sub> interspersed	No change in SC/Type I fiber  No change in SC/Type II fiber  ++ Pax7+ /MyoD+	33

		with 10 s of rest	cells/Fiber (active SC)  ++ Pax7- /MyoD+ cells/Fiber  (differentiating SC)	
Human, males and females (n=9)	21±4 yr	MICT 6 wk, 4 d/wk on cycle ergometer 30 min @ 65% $\dot{V}O_{2peak}$	No change in SC/Type I fiber  No change in SC/Type II fiber  ++ Pax7+ /MyoD+ cells/Fiber (active SC)  ++Pax7- /MyoD+ cells/Fiber  (differentiating SC)	33
Human, females (n=7)	56±5 yr	END 12 wk, 3 d/wk on cycle ergometer 45 min @ 65% $\dot{V}O_{2max}$	No change in SC/Type II fiber  ++SC/Type I fiber  ++ SC/Total fiber	30
Wistar rats, male, plantaris (n=12)	5 wk	8 wk, voluntary wheel running	++SC/Total fibers	22
Wistar rats, male (n=10) and female (n=10), gastroc	3.5 months	END 13 wk, 6 d/wk on treadmill, 20 min sessions @ 0.5 km/h (moderate intensity)	++SC/Total fibers	26
Wistar rats, male (n=9) and female (n=8), gastroc	Males: 15- 17 months  Females:	END 13 wk, 6 d/wk on treadmill, 20 min sessions @ 0.5 km/h	++SC/Total fibers	26

	15 months	(moderate intensity)		
Sprague-Dawley rats, female, plantaris (n=9)	10 wk	Low intensity END training 10 wk on treadmill, 30 min sessions 5 d/wk graded increase (speed 25-30m/min; grade 0%-3%).	No change in SC/Total fiber	23
Sprague-Dawley rats, female, plantaris (n=9)	10 wk	Low intensity END training 10 wk on treadmill, 90 min sessions 5 d/wk graded increase (speed 25-30m/min; grade 0%-3%).	No change in SC/Total fiber	23
Sprague-Dawley rats, female, plantaris (n=9)	10 wk	high intensity END training 10 wk on treadmill, 30 min sessions 5 d/wk graded increase (speed 25-30m/min; grade 0%-18%).	++ SC/Total fiber	23
Sprague-Dawley rats, female,	10 wk	high intensity END training 10 wk on	No change in SC/Type I fiber ++ SC/Total fiber	23



plantaris (n=9)		treadmill, 90 min sessions 5d/wk graded increase (speed 25-30m/min; grade 0%-18%).	++ SC/Type II fiber	
NES-GFP heterozygous C57Bl/6 male mice EDL	Young: 4 months (n=7) Old: 16 months (n=6)	Moderate intensity END 8 wk on treadmill, 30min/d, 6d/wk @ 11.5m/min	++ SC/Total fiber	25
C57Bl/J male mice, (n=6)	24 months	Progressive END training 8 wk, on treadmill, 3 d/wk, 40 min/session (speed 8.5 – 15 m/min).	++ SC/Total fiber	24

END, endurance; EDL, extensor digitorum longus; gastroc, Gastrocnemius;  $HR_{max}$ , heart rate maximum; MICT, moderate intensity continuous training; SIT, sprint interval training;  $\dot{V}O_{2peak}$ , peak oxygen uptake.